(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/006692 A1

(51) International Patent Classification[7]: A23L 1/29, 1/308, A61K 9/14

(21) International Application Number: PCT/GB2003/003040

(22) International Filing Date: 11 July 2003 (11.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0216147.9 12 July 2002 (12.07.2002) GB

(71) Applicant (*for all designated States except US*): **RECKITT BENCKISER HEALTHCARE (UK) LIMITED** [GB/GB]; 103-105 Bath Road, Slough, Berkshire SL1 3UH (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **DETTMAR, Peter, William** [GB/GB]; Tithe House, Tithe Barn Lane, Patrington, East Yorkshire HU12 0PE (GB). **HAVLER, Michael, Edward** [GB/GB]; Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull HU8 7DS (GB). **MCKIE, Kevin** [GB/GB]; 33 Northolme Road, Hessle, East Yorkshire HU13 9HR (GB).

(74) Agents: **HALL, Marina** et al.; Reckitt Benckiser plc, Group Patents Department, Dansom Lane, Hull HU8 7DS (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/006692 A1

(54) Title: IMPROVED BULKING AGENT COMPOSITIONS

(57) Abstract: The present invention provides an ingestible composition comprising a fibre or saccharide bulking agent, an ingestible silica, and an ingestible surfactant. The provision of the silica and the surfactant provides a synergistic benefit in the dispersal of the bulking agent in water thus making it easier and/or quicker to obtain an imbibable liquid. The bulking agent may be ispaghula, a natural material of benefit in promoting good bowel function.

Improvements In and Relating to Medicinal Compositions

The present invention relates to medicinal compositions comprising fibre bulking agents.

Ingestible fibre- compositions for the relief of gastric and digestive dysfunctions are known. Examples of such compositions include granular psyllium husk fibre (ispaghula) intended to be stirred in measured amounts into a volume of liquid, usually water or soft drinks. After stirring, the drinking composition is intended to be quickly imbibed due to the propensity of the ispaghula to absorb water readily and swell to form a viscous gel-like mass. It is the property of water absorption which has the desired characteristic of fibre or saccharide-containing ingestible compositions for gastric and digestive dysfunctions. Once the fibre or saccharide-containing composition has absorbed water to produce the gel-like mass, the mass is relatively insoluble and fibrous, and is transported through the gut quickly with minimal digestion, helping to alleviate constipation and other digestive dysfunctions.

Other forms, such as capsules forms for ingestion, are also available, such capsules being designed to be broken down in the gut, wherein the released fibre or saccharide bulking agent absorbs water from the gut to form the viscous mass.

However, for beneficial ease-of-use properties, a particulate form is particularly advantageous to the end user, as this can be stirred into a volume of liquid, for a more pleasant taste, and the granular form of the fibre

absorbs water from the gut more quickly than a capsule form. However, there are a number of problems involved in using a granular form of the fibre-containing ingestible compositions.

Primarily, it is desirable for the ingestible compositions to disperse easily in liquid, for the user's convenience and/or so that the resultant drink is more palatable and/or easier to swallow. Any new composition must be as good as or, preferably, better than, existing compositions in this respect.

Secondly, the handling of some ingestible fibre-containing compositions is not straightforward. For example in commercial production ispaghula is milled then isopropyl alcohol and a granulating agent polyvinyl pyrollidone are added. These steps aid handling of the compositions during manufacturing, before the isopropyl alcohol is removed prior to packaging the product for sale. The granulation also aids the dispersion of the ispaghula into a volume of liquid, prior to ingestion. However, the use of the granulating agent and isopropyl alcohol increases the cost of production and the use of the isopropyl alcohol is undesirable from an environmental and a health and safety perspective.

Thus, from the foregoing, it is apparent that there is a need for the provision of an ingestible composition which comprises a fibre bulking agent, in which the ingestible composition disperses easily in an aqueous liquid and/or is of improved manufacture.

It has now been determined that an ingestible composition comprising a psyllium husk fibre bulking agent (ispaghula), colloidal silica in conjunction with an ingestible surfactant, can offer benefit in the manufacture of the ingestible composition, and can increase the rate at which the ingestible composition disperses in water or other ingestible liquid.

Therefore, according to the present invention there is provided an ingestible composition comprising ispaghula, colloidal silica and an ingestible surfactant wherein said composition is in a form so that in use it is dispersed in a liquid prior to ingestion.

The presence of both an ingestible silica and an ingestible surfactant can confer significant, eg synergistic, benefits. For example, the ternary composition of the ispaghula has outstanding wettability properties, and is easy to manufacture, for example by simple blending.

Suitably the fibre bulking agent is a natural ingestible fibre (by which term we include herein fibre extracts). Plant-derived fibre bulking agents from psyllium husk fibre (ispaghula) are used.

The ispaghula may comprise whole ispaghula seeds, but preferably at least part of the ispaghula comprises separated ispaghula seed husks. More preferably the ispaghula comprises at least 50% wt separated ispaghula husks, most preferably at least 95% wt separated ispaghula husks. Suitably the remainder of the ispaghula comprises other seed parts and/or other ispaghula plant materials. In preferred compositions the seed kernels themselves have been substantially removed to leave the husks.

Suitably the fibre bulking agent is present in the ingestible composition in an amount of at least 10wt%, preferably at least 30wt%, and most preferably at least 40wt% of the total weight of the ingestible composition.

Suitably the fibre bulking agent is present in the ingestible composition in an amount up to 90wt%, preferably up to 80wt%, and most preferably up to 75wt% of the total weight of the ingestible composition.

ART 34 AMDT

Suitably the colloidal silica is fumed or precipitated synthetic or natural silica. The silica may be amorphous or crystalline.

Suitably the mean particle size of the silica is at least 5nm, preferably at least 10nm.

Suitably the mean particle size of the silica is up to 5μm, preferably up to 0.75μm, more preferably up to 0.5μm, and most preferably up to 0.2μm.

One suitable silica material is Syloid 244 which is amorphous silica, has a mean particle size of about 3μm and is provided by W R Grace & Co. Another suitable silica materials is Silox 15,also from W R Grace & Co., and which has a mean particle size of about 4μm.

Another suitable silica material is Huber Zep 49 which is amorphous silica from J M Huber Corporation and contains about 1 wt% alumina.

Another suitable silica is Aerosil 200 from Degussa Company. It contains less than 0.05 wt% alumina and has a mean particle size of 12 nm.

The silica is colloidal silica (silicon dioxide), and a preferred silica is a colloidal silica which is sold under the trade mark CAB-O-SIL, by Cabot Inc, USA.

Suitably the specific surface area of the silica is at least $50m^2\ g^{-1}$, preferably at least $150m^2\ g^{-1}$.

Suitably the specific surface area of the silica is up to $400m^2\ g^{-1}$, preferably up to $300m^2\ g^{-1}$ most preferably up to $200m^2\ g^{-1}$.

Suitably the silica is present in the ingestible composition in an amount at least 0.01wt%, preferably at least 0.05wt%, more preferably at least 0.1wt% and most preferably at least 0.25wt%, of the total weight of the ingestible composition.

The upper limit of silica in the ingestible composition may be up to 11 wt%. Suitably the silica may be present in the ingestible composition in an amount up to 5wt%, preferably up to 2wt%, more preferably up to 1wt%, and most preferably up to 0.6wt%, of the total weight of the ingestible composition.

Preferably the ingestible surfactant is a polyethylene-, polypropylene-, or polyoxyethylene-based surfactant. Suitable polyethylene or polyoxyethylene-based surfactants include polyethylene glycols and polyoxyethylene sorbitan fatty acid esters (polysorbates).

Suitable polyethylene glycols have a molecular weight of between 200 and 40,000, preferably between 200 and 1,000, and more preferably between 200 and 600. Suitable

polyethylene glycols include MACROGOLD and MACROGOLUM polyethylene glycols sold by ICI Surfactants, UK. Other suitable surfactants include polyoxyethylene monostearates and glycerol polyethylene glycol oxystearates.

Suitably the surfactant is present in the ingestible composition in an amount at least 0.01wt%, preferably at least 0.05wt%, more preferably at least 0.1wt%, and most preferably at least 0.2wt%, of the total weight of the ingestible composition.

Suitably the surfactant is present in the ingestible composition in an amount up to 5wt%, preferably up to 3wt%, more preferably up to 2wt% and most preferably up to 1wt%, of the total weight of the ingestible composition.

When the surfactant is polyethylene glycol it is preferably present is an amount at least 0.1wt%, more preferably at least 0.3wt%, of the total weight of the ingestible composition.

When the surfactant is polyethylene glycol it is preferably present is an amount up to 2wt%, more preferably up to 1.5wt%, of the total weight of the ingestible composition.

When the surfactant is a polyoxyethylene sorbitan fatty acid ester it is preferably present in an amount at least 0.01wt%, more preferably at least 0.05wt%, and most preferably at least 0.08wt%, of the total weight of the ingestible composition.

When the surfactant is a polyoxyethylene sorbitan fatty acid ester it is preferably present in an amount up to 2wt%, more preferably up to 1wt%, and most preferably up to 0.5wt%, of the total weight of the ingestible composition.

The percentages stated represent the total complement of the silica and surfactant, that is, summated if there is more than one silica or surfactant in the composition.

The ingestible composition may further comprise ingestible co-ingredients such as a bicarbonate for example sodium bicarbonate, an ingestible acid, for example citric acid, a flavouring, or a colouring, for example.

Preferably the ingestible composition does not contain a granulating agent.

Most preferably the ingestible composition does not contain polyvinyl pyrollidone.

Preferably the ingestible composition does not contain any residue of polyvinyl alcohol.

The composition is particularly preferred in a form such that it is easily dispersed in a liquid such as water before drinking. Suitably the composition is provided in a particulate or granular solid form, for example as a powder or flakes, intended to be mixed with water, prior to ingestion by a user. Alternatively the composition may be provided as a capsule for dispersal in a liquid, for drinking by a user. Preferably the composition is provided in a particulate form.

In accordance with a second aspect of the present invention there is provided a method of making an ingestible composition comprising a fibre or saccharide bulking agent, an ingestible silica, and an ingestible surfactant, the method comprising the step of blending the fibre or saccharide bulking agent with the ingestible silica and the ingestible surfactant.

Preferably no isopropyl alcohol is used in the manufacture.

More preferably no solvent of any type is used in the manufacture.

Preferably no polyvinyl pyrollidone is used in the manufacture.

More preferably no granulating agent of any type is used in the manufacture.

The fibre or saccharide bulking agent may be milled prior to the blending step, suitably to a mean particle size in the range 250-450μm.

Preferably the method does not include the granulation of the bulking agent.

The fibre or saccharide bulking agent may be subjected to a sterilization step prior to the blending step. Irradiation may employ steam or, preferably, a radioactive source, for example a γ-radiation source, for example from

a Cobalt-60 or Caesium-137 source. A suitable radiation dosage is up to 13 kGy, preferably 5-10 kGy.

The invention will now be described by way of example in which the following materials are used throughout:

Ispaghula - Ispaghula husk material obtained from *Plantago ovata*, broken down to enable the seed kernels to be removed. The material was dried, irradiated with γ-radiation from a Caesium-137 source at a dosage rate of about 7 kGy, as described in PCT/GB01/02040, and milled to a mean particle size of 300-400μm.

CAB-O-SIL (Trade Mark) - A colloidal silica having a specific surface area in the range $175\text{-}225 m^2g^{-1}$ manufactured by Cabot Inc, USA.

TWEEN 60 (Trade Mark) - A polyoxyethylene sorbitan fatty acid ester, manufactured by ICI.

TWEEN 80 (Trade Mark) - A polyoxyethylene sorbitan fatty acid ester, manufactured by ICI.

Propylene glycol.

Cremophore RH40 - Glycerol polyethylene glycol oxysterate, manufactured by BASF.

Pricerine - Porcine glyerine, supplied by Uniquema.

PEG 200 - Polyethylene glycol, molecular weight approximately 200, manufactured by Clariant.

Liquid surfactants were added slowly to the ispaghula as it was being mixed in a domestic-style MAGIMIXER (Trade Mark). Mixing was continued until the ispaghula appeared evenly covered (dampened).

Solid surfactants were ground in a pestle and mortar and then added to the ispaghula and placed in an oven (60-70°C) for 30 minutes. The samples were then quickly blended in the MAGIMIXER as above.

To the ispaghula blended with surfactant as described above was added a colloidal silica sample (CAB-O-SIL) in an attempt to dust the samples dry and improve flow characteristics (but also - as will be seen - with the unexpected result that the wetting characteristics of the final product were greatly improved).

No granulation step took place; no granulating agent was used.

Test methods

1. Wettability (dispersion in water)

This was the most important test used to assess the effectiveness of each treatment and simply involved slowly spreading an amount of the formulation containing 3.5g ispaghula onto the surface of 150ml of cold tap water contained in a 200ml Pyrex beaker, and recording the time taken for all the material to become fully wetted without using any agitation to quicken the process.

2. Water absorbency/swell volume

This test determines the swell volume (ml) or ability of a product to take up water. This is a key property for the mechanism of action of ispaghula, and hence disruption/reduction to this effect would certainly impact on efficiency.

The method is as follows:

Add 1g of ispaghula (or the equivalent wt of product containing 1g ispaghula) to 100ml of tap water in a 100ml measuring cylinder, mix thoroughly by shaking and allow to stand. At 1 and 2 hours mix again by gentle inversion, and allow to stand for a further 2 hours. At the end of this period (4 hours from start), record the level of mucilage/gel in the measuring cylinder. Typically, this will be 40-50ml per gramme of ispaghula.

3. Gel/flow rate on hydration

This method is used to gain an insight into the rate of gel/mucilage formation. Although gelling is an important attribute, the initial onset has been delayed in ingestible ispaghula compositions to allow the consumer to ingest it, over a period of a few minutes, as a palatable drink.

A weight of sample containing 3.5g ispaghula is mixed into 150ml cold tap water in a 200ml beaker. At 5 minute intervals after making up, the time taken for 100ml of the sample to run through a Flow Cup (No. 5) viscometer is recorded. This is basically a brass cup which holds exactly 100ml, with a tapered bottom leading to a standard-sized hole. As a sample gels, then the time taken for 100ml to flow through increases.

4. Carr's Index

Carr's index is a measurement of bulk density of pharmaceutical powders, measured in a Copley Erweka Tapped Volumeter, model SVM-22. Powder is placed in a vertical cylinder which is "tapped" in the machine to aid the settlement of the powder, and the percentage change in volume measured, over the predetermined test period/regime, identical for each sample.

Example 1

In this series of tests the wetting ability of ternary ispaghula + PEG 200 + CAB-O-SIL compositions was assessed, and compared with non-ternary compositions. The

wettability was measured after 5 minutes, 16-24 hours and 8 days; there is reason from work on other compositions to believe that wettability can decrease as the interval from manufacture increases.

As will be seen, there were three replicates. All three results are given in Tables 1-3 below.

In each test the measurement was of time (secs) for a dose of treated ispaghula (3.5g) to disperse.

Tables 1-3

PEG 200 + CAB-O-SIL 5 mins after manufacture

	CAB-O-SIL levels (wt%)	
PEG 200 levels (wt%)	0.3	0.5
0.4	5,5,5	7,5,6
0.8	7,8,7	6,5,5
1.2	6,4,4	6,7,7

Comparisons: no PEG 200, no CAB-O-SIL: 270, 310, 330
no PEG 200, 0.3 wt% CAB-O-SIL: 165, 170, 165
0.4 wt% PEG 200, no CAB-O-SIL: 120, 130, 135

PEG 200 + CAB-O-SIL 16-24 hours after manufacture

	CAB-O-SIL levels (wt%)	
PEG 200 levels (wt%)	0.3	0.5
0.4	6,6,6	7,5,7
0.8	20,20,20	6,5,6
1.2	11,12,11	12,11,12

Comparisons: no PEG 200, no CAB-O-SIL: not measured
no PEG 200, 0.3 wt% CAB-O-SIL: 330, 330, 350
0.4 wt% PEG 200, no CAB-O-SIL: 305, 320, 320

PEG 200 + CAB-O-SIL 8 days after manufacture

	CAB-O-SIL levels (wt%)	
PEG 200 levels (wt%)	0.3	0.5
0.4	11,12,11	10,6,7
0.8	25,25,30	8,8,8
1.2	22,30,26	15,17,15

Comparisons: no PEG 200, no CAB-O-SIL: 310, 300, 280
no PEG 200, 0.3 wt% CAB-O-SIL: 1800, 1200, 1740
0.4 wt% PEG 200, no CAB-O-SIL : 470, 480, 510

Example 2

This series of tests were as Example 1, but used TWEEN 80 instead of PEG 200, and different time intervals. In

these tests ispaghula alone was not tested. The results are given in Tables 4-6 below. Again, in each test the measurement was of time (secs) for a dose of treated ispaghula (3.5g) to disperse (n=3).

Tables 4-6

TWEEN 80 + CAB-O-SIL 5 mins after manufacture

	CAB-O-SIL levels (wt%)	
TWEEN 80 levels (wt%)	0.3	0.5
0.09	21,16,17	20,17,20
0.14	7,7,8	8,5,8
0.20	4,4,5	4,4,4

Comparisons: no TWEEN 80, no CAB-O-SIL: not measured
no TWEEN 80, 0.3 wt% CAB-O-SIL: 180, 215, 225
0.09wt% TWEEN 80, no CAB-O-SIL : 75, 80, 75

TWEEN 80 + CAB-O-SIL 72 hours after manufacture

	CAB-O-SIL levels (wt%)	
TWEEN 80 levels (wt%)	0.3	0.5
0.09	25,25,30	30,22,25
0.14	10,13,11	10,10,9
0.20	6,5,4	4,5,5

Comparisons: no TWEEN 80, no CAB-O-SIL: not measured
no TWEEN 80, 0.3 wt% CAB-O-SIL: 495, 450, 480
0.09wt% TWEEN 80, no CAB-O-SIL : 63, 70, 60

TWEEN 80 + CAB-O-SIL 7 days after manufacture

	CAB-O-SIL levels (wt%)	
TWEEN 80 levels (wt%)	0.3	0.5
0.09	36,27,32	35,35,35
0.14	10,10,12	10,9,8
0.20	7,7,6	4,5,5

Comparisons: no TWEEN 80, no CAB-O-SIL: not measured
no TWEEN 80, 0.3 wt% CAB-O-SIL: 735, 795, 930
0.09wt% TWEEN 80, no CAB-O-SIL : 75, 67, 78

Again the results for the ternary system are remarkable, much better than either binary system.

Example 3

This test was used primarily to assess long term wettability properties. Obviously such properties are extremely important for a commercial product.

As before, each experiment employed 3.5g of ispaghula in the composition, except that for the swell volume test 1g of composition was used.

The compositions were placed in a cycling oven, cycling between 4°C and 30°C. The samples were tested immediately on preparation, after 5 weeks incubation in the cycling oven, and after 3 months incubation the cycling oven. As an exception, compositions including CAB-O-SIL and PEG 200

were tested immediately and after 9 weeks incubation only. The results of the experiment are shown in Table 7.

Table 7

Storage conditions – Cycling Oven (4°C/30°C)

	Initial samples				5 week samples			3 month samples		
Composition	Carrs Index (n=2)	Swell Vol (ml) (n=2)	Wettability times (secs)	Flow cup after 15 min (secs)	Swell Vol (ml) (n=2)	Wettability times (secs)	Flow cup after 15 min (secs)	Swell Vol (ml) (n=2)	Wettability times (secs)	Flow cup after 15 min (secs)
Untreated Ispaghula			270							
+ 0.16wt% TWEEN 80 + 0.08wt% CAB-O-SIL	9	40	23	45	44	19	35	37	19	61
+ 0.16wt% TWEEN 60 + 0.08wt% CAB-O-SIL	9	40	20	25	44	19	52	42	22	52
+ 0.4wt% Propylene glycol + 0.08wt% CAB-O-SIL	6	40	44	25	44	60	18	43	81	59
+ 1.2wt% Cremophore + 0.24wt% CAB-O-SIL	7	40	25	25	41	19	33	44	32	46
+ 0.4wt% Pricerine + 0.4wt% CAB-O-SIL	7	41.5	50	35	45	120	21	41	211	62
								9 weeks storage		
+ 0.56wt% PEG 200 + 0.24wt% CAB-O-SIL	9	41	15	35				47	27	48

The results show that the addition of all of the tested combinations of ingestible silica in combination with an ingestible surfactant, substantially reduces the time taken for the ispaghula to disperse in a 150ml beaker of cold water (wettability). The wettability time is significantly reduced on initial testing and remains reduced through the 5 week samples and the 3 month samples.

In particular, polyethylene glycol and TWEEN in combination with CAB-O-SIL show a marked ability to reduce the wettability time of untreated ispaghula husk compared to other combinations of surfactant with CAB-O-SIL. The results therefore indicate that ingestible compositions comprising surfactant plus CAB-O-SIL mixed with ispaghula husk are also shelf stable at ambient temperatures (between 4°C and 30°C) over a sustained period of time.

Example 4

The tests corresponded to those of Example 3 but the compositions were tested by incubating at 40°C in an incubating oven. The samples were tested immediately on preparation, after 5 weeks incubation and after 3 months incubation. As an exception, compositions containing CAB-O-SIL and PEG 200 were tested immediately and after 9 weeks incubation only. The results of the experiment are shown in Table 8.

Table 8

Storage conditions: 40°C

	Initial samples				5 week samples			3 month samples		
Composition	Carrs Index (n=2)	Swell Vol (ml) (n=2)	Wettability times (secs)	Flow cup after 15 min (secs)	Swell Vol (ml) (n=2)	Wettability times (secs)	Flow cup after 15 min (secs)	Swell Vol (ml) (n=2)	Wettability times (secs)	Flow cup after 15 min (secs)
Untreated Ispaghula			270							
+ 0.16wt% TWEEN 80 + 0.08wt% CAB-O-SIL	9	40	23	45	44	20	18	46	17	40
+ 0.16wt% TWEEN 60 + 0.08wt% CAB-O-SIL	9	40	20	25	44	22	21	50	16	31
+ 0.4wt% Propylene glycol + 0.08wt% CAB-O-SIL	6	40	44	25	42	85	23	47	110	28
+ 1.2wt% Cremophore + 0.24wt% CAB-O-SIL	7	40	25	25	41	20	45	37	26	30
+ 0.4wt% Pricerine + 0.4wt% CAB-O-SIL	7	41.5	50	35	43	180	35	50	364	41
+ 0.56wt% PEG 200 + 0.24wt% CAB-O-SIL	9	41	15	35				9 weeks storage 47	26	23